

BEFORE THE BOARD OF APPEALS AND INTERFERENCES  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 10/613,380

Customer No. 23379

Applicant: Wendell Lim, et al.

Confirmation No. 5261

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Group Art Unit: 1631

Docket No. UCSF03-114

Examiner: Skibinsky, Anna

Title: *Protein Logic Gates*

REPLY BRIEF

Honorable Board of Appeals and Interferences  
United States Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Honorable Board:

The Answer (Nov 16, 2007) reproduces the enablement rejection of the Nonfinal Action (Jul 30, 2007), which was reproduced from the previously appealed-from Final Action (Nov 30, 2006). Accordingly, we maintain our appeal from the Nonfinal Action, which reopened prosecution in response to our prior Appeal Brief (Mar 11, 1007), because the Examiner's arguments are inconsistent with the Specification and evidence of record.

The uncontroverted evidence of record documents that world-renowned authorities independently concluded that Appellants' data "pave the way" for creating alternative signal-response elements by protein design (Adler et al. Signaling Breakthroughs of the Year. Adler, Gough, and Ray (2004) Science's STKE 2004: et1-1; of record). Unable to rebut this evidence, the Examiner declines to address it.

The uncontroverted evidence of record confirms that the Specification provides adequate guidance to permit one skilled in the art to practice the invention as claimed without undue experimentation (Declaration by Dr. Henry Bourne; of record). Unable to rebut this evidence, the Examiner declines to address it.

The uncontroverted evidence of record documents that those skilled in the art have in fact followed the guidance of this disclosure and without resorting to undue experimentation built numerous switches (Declaration by Dr. Henry Bourne, esp. p.3, lines 7-20; of record). Unable to rebut this evidence, the Examiner declines to address it.

Faced with a record inconsistent with her rejection, the Examiner now attempts to alter the record. First, she cites in her Answer for the first time in this application a new reference, a post-filing date publication by the inventors, only to exalt in bold letters two word-pairs taken embarrassingly out of context. By even a cursory read, the contextual sentences (beginning at p.1906, col.2, line 9; and p.1906, col.3, line 8, respectively) do not restrict the generality of the autoregulated fusion proteins, but rather provide additional levers for the practitioner to create alternative outputs. Of course, the Examiner steers clear of the rest of her newly cited paper, including its concluding paragraphs, which exalt the generality of the findings:

These results demonstrate that multidomain signaling switches like N-WASP are functionally modular; diverse and complex gating behaviors can be generated through relatively simple recombination events between input and output domains, even among domains with no known evolutionary relation. By allowing the establishment of novel regulatory connections between molecules with no previous physiological relation, such recombination events would be a powerful force driving evolution of novel cellular circuitry (18). This interchangeability exists because, in modular allosteric switches, regions that mediate input control are physically separable from output regions. Facile interchange of gating properties is unlikely to occur in conventional allosteric proteins in which input and output activities are centralized in a single folded structure, and gating is mediated by subtle conformational shifts.

Domain recombination space sampled in these experiments proved functionally rich: Although constructs showed a range of different gating behaviors (negative-positive, integrating-nonintegrating, etc.), nearly all of them show some form of gating. Gating as an emergent property, therefore, does not appear to be extremely rare, as might be expected if only very precise domain arrangements yielded regulation. This modular framework, in addition to promoting switch protein evolution, could be used to engineer proteins with novel regulatory control and, in principle, novel cellular circuits.

The Examiner's citation of two word-pairs from one post filing publication of the inventors is the epitome of irony, because (as the Examiner has no doubt learned) the post-filing date literature is rife with diverse demonstrations of the claimed autoregulated fusion proteins by numerous groups, including Appellants. Though the rules asymmetrically permit an Examiner to enlarge the record in her Answer, while not allowing Appellants to respond with rebuttal evidence, we encourage the Board to independently verify the foregoing: a good starting point is the list of

publication links at Professor Lim's UCSF homepage, which may be found by with any search engine (keyword, "Limlab"). By way of example, a few months after the inventors published the Science paper cited by the Examiner, they published "Rewiring cell signaling: the logic and plasticity of eukaryotic protein circuitry", Dueber, et al. Current Opinion in Structural Biology 2004, 14:690–699, abstracted as follows:

Living cells rival computers in their ability to process external information and make complex behavioral decisions. Many of these decisions are made by networks of interacting signaling proteins. Ongoing structural, biochemical and cell-based studies have begun to reveal several common principles by which protein components are used to specifically transmit and process information. Recent engineering studies demonstrate that these relatively simple principles can be used to rewire signaling behavior in a process that mimics the evolution of new phenotypic responses.

Finally, and without belaboring the issue, we trust the Board will recognize that the strawmen that the Answer erects on page 10-11 as "Appellant's Position" and "Appellant's Arguments" – ripe with the Examiner's own misspellings, grammatical errors, and incomprehensible sentences – are not Appellant's position and arguments.

Appellants respectfully request reversal of the subject enablement rejection by the Board of Appeals.

Respectfully submitted,  
Science & Technology Law Group

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